## REMARKS

Claims 59 and 68-78 are pending in this application. Claims 51, 53, 54 and 56 have been canceled herein without prejudice or disclaimer. Claims 59 and 68-77 have been amended, and new claim 78 has been added.

Applicant submits that no new matter is added by these amendments. Support for the amendments to the claims is indicated as follows:

Claim 59 has been amended in clauses (c) and (d) to clarify that the measuring steps involve "adding a first anti-thyroglobulin antibody capable of binding to both types of the thyroglobulin". A similar amendment is made in claims 69 and 73. Support for these amendments may be found in the specification, for example, on page 5, 1st full paragraph and last paragraph, and page 7, 3rd full paragraph.

Claim 69 (clause (e)), claim 70 (clause (e)), claim 71 (clause (f)), claim 72 (clause (e)), claim 73 (clause (d)), claim 74 (clause (f)), and claim 75 (clause (d)) have also been amended to clarify which type of thyroglobulin is being measured, with reference to preceding clauses.

Claims 59 and 68-78 have been amended in the last clause to recite that:

> "the sample is determined to be malignant in any of the following cases (i) to (iv),
>
> (i) when the calculated ratio is significantly higher than that of the reference fluid sample of the normal thyroid and is significantly higher than that of the reference fluid sample of the benign thyroid,
>
> (ii) when the calculated ratio is significantly lower than that of the reference fluid sample of the normal thyroid and is significantly lower than that of the reference fluid sample of the benign thyroid,
>
> (iii) when the calculated ratio is significantly higher than that of the reference fluid sample of the normal thyroid and is significantly lower than that of the reference

> fluid sample of the benign thyroid, or
>
> (iv) when the calculated ratio is significantly lower than that of the reference fluid sample of the normal thyroid and is significantly higher than that of the reference fluid sample of the benign thyroid."

Clauses (i) and (ii) are supported by Figures 1 and 2 of the present application. Clauses (iii) and (iv) are supported by Figure 3.

New claim 78 is supported by claim 70, but lacks the separation step recited as step (b) in claim 70. Support for new claim 78 may also be found in the specification on page 9, lines 9-23, and on page 11, line 25, to page 12, line 12.

**Claims 51, 53, 56, 59 and 68-77 are/remain rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement for the reasons of record.** (Office action paragraph no. 6)

The rejection is moot for claims 51, 53 and 56, which have been canceled without prejudice or disclaimer. The rejection of claims 59 and 68-77 is overcome by the amendments to the claims.

In the rejection, the Examiner refers to written support for the recitation regarding when the sample is determined to be malignant. As noted above, the claims have been amended to recite that:

> "the sample is determined to be malignant in any of the following cases (i) to (iv),
>
> (i) when the calculated ratio is significantly higher than that of the reference fluid sample of the normal thyroid and is significantly higher than that of the reference fluid sample of the benign thyroid,
>
> (ii) when the calculated ratio is significantly lower than that of the reference fluid sample of the normal thyroid and is significantly lower than that of the reference

> fluid sample of the benign thyroid,
>
> (iii) when the calculated ratio is significantly higher than that of the reference fluid sample of the normal thyroid and is significantly lower than that of the reference fluid sample of the benign thyroid, or
>
> (iv) when the calculated ratio is significantly lower than that of the reference fluid sample of the normal thyroid and is significantly higher than that of the reference fluid sample of the benign thyroid."

Support for the four conditions which lead to a determination of malignancy may be found in the present application as follows: Clauses (i) and (ii) are supported by Figures 1 and 2 of the present application. Clauses (iii) and (iv) are supported by Figure 3.

Applicant submits that this wording is therefore fully supported by the application, as filed. Reconsideration of the rejection is respectfully requested.

**Claims 51, 53, 54, 56, 59 and 68-77 are/remain rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement for the reasons of record.** (Office action paragraph no. 7)

The rejection is moot for claims 51, 53, 54 and 56, which have been canceled without prejudice or disclaimer. The rejection of claims 59 and 68-77 is respectfully traversed.

In the rejection, the Examiner refers to the wording regarding "specific antibodies capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin."

Applicant again argues that support for the recitation of the claims can be found in the specification, and that the rejection is based on the Examiner's indication of a lack of working examples. Applicant again notes, for example, the disclosure in the specification of "protein binding

to a specific sugar chain structure" on page 6, line 7, to page 7, line 13. These lines include a specific discussion of the meaning of "capable of binding to a sugar chain structure" on page 6, last paragraph, though page 7, line 13.

The Examiner refers to Applicant's "contemplation of antibodies" on page 6 of the specification, stating that "the specification fails to teach that any of the specific antibodies would be useful ..." (page 5, line 6, of the Office action). The Examiner appears to be comparing the amount of disclosure in the specification of examples of lectins, for example the disclosure on page 6, lines 9-23, with the amount of disclosure on antibodies.

However, Applicant submits that, given how antibodies are prepared by one of skill in the art, such a comparison is inappropriate. The specification clearly states how the antibodies capable of binding to a specific sugar chain structure are made, on page 7, lines 3-6. Applicant submits that this a completely adequate written description of these antibodies. Reconsideration of the rejection is therefore respectfully requested.

**Claims 51, 53, 54, 56, 59, 68, 69 and 74 remain rejected under 35 U.S.C. §103(a) as being unpatentable over either Nakamura (U.S. Patent 5,571,729) or Satomura (U.S. Patent 5,780,247) in view of either Yamamoto (of record), Tarutani (of record) or Survilo for reasons of record.** (Office action paragraph no. 8)

The rejection of claims 51, 53, 54 and 56 is moot in view of the cancellation of these claims without prejudice or disclaimer. The rejection of claims 59, 68, 69 and 74 is respectfully traversed.

In traversing the rejection, Applicant summarizes the difference between the pending claims and cited references:

Nakamura and Satomura

Nakamura and Satomura teach methods for measuring the amounts of different types of glycoproteins that are different with respect to their pectin reactivity, and also the total amounts of the glycoprotein of interest.

However, Nakamura and Satomura **do not disclose or suggest the measurements of thyroglobulin**. They do not teach any relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor. Determination of malignancy of thyroid tumor is not disclosed. Further, Nakamura and Satomura **do not teach nor suggest a comparison to benign thyroid adenoma**.

Yamamoto

Yamamoto teaches that thyrogobulin isolated from malignant thyroid tumor tissue has a different DEAE-cellulose ion exchange elution pattern from thyroglobulin isolated from benign and from normal thyroids.

However, Yamamoto does not show the measurement of an amount of thyroglobulin. In page 135, Fig. 1 of Yamamoto, human thyroglobulin was purified, digested by the action of exhaustive pronase, subjected to DEAE-cellulose ion exchange chromatography (Yamamoto, page 133, column 2, MATERIALS AND METHODS, *Isolation of oligosaccharides from human*

*thyroglobulin*, page 134, column 1, *fractionation of oligosaccharides*). In page 139, Fig. 5 of Yamamoto, purified thyroglobulin was **digested by the action of exhaustive pronase**, subjected to DEAE-cellulose ion exchange chromatography, eluted with a linear concentration gradient of NaCl, subjected to Con A-Sepharose chromatography and RCA-Sepharose chromatography (page 134, column 1, *Fractionation of oligosaccharides*). That is, Yamamoto shows that the elution pattern of **digested product** of thyroglobulin from a malignant thyroid tissue is compared with that of digested product of thyroglobulin from normal thyroid tissue. However, **Yamamoto does not measure the amount of thyroglobulin, nor compare an amount of thyroglobulin itself from a malignant thyroid tissue with that from a normal thyroid issue or benign thyroid tissue.**

Determination of malignancy of thyroid tumor is not disclosed, either. Further, Yamamoto does not teach nor suggest comparison to benign thyroid adenoma.

Tarutani et al.

Examiner asserts that Tarutani teaches that the percent of total thyroglobulin that binds to Con A is different from trabecular carcinoma compared to either follicular adenoma (a benign condition) or normal thyroid tissue.

However, in Tarutani, **soluble protein** extracted in the buffer is obtained, and the protein is regard as Tg. Therefore, **the determined amount protein is not equal to the amount Tg itself** in Tarutani.

Tarutani discloses the following:

Thyroid tissues are sliced and soluble proteins are extracted (page 852, "MATERIALS AND METHODS, *Thyroid Glands*"). The obtained extract is passed through a column packed with Con A, etc., whereby ingredients contained in the extract are separated on a chromatography. And, it is predicted that carbohydrate structures are different between normal Tg and tumor Tg, in particular:

> "Thyroid tissues were sliced and soluble proteins were extracted in the buffer used for the con A-gel affinity chromatography. The supernatant, obtained after centrifugation, was used to prepare thyroglobulin." (page 852, left column, "*Thyroid Glands*")
>
> "A solution of the thyroid extract was applied to the column, and the unabsorbed protein was removed by extensive washing with the buffer. Protein absorbed on the column was eluted with MeG dissolved in the buffer." (page 852, left column, "*Isolation of thyroglobulin on a Concanavalin A-Sepharose column*")

Tarutnai obtained the amount of Tg by calculating on the basis of $E^{1\%\text{-}1cm,}{}_{280nm}$ of the purified sample solution (Tarutani, page 852, column 2, lines 1 to 2). Tarutani measures the amount of the soluble protein in the sample, but this amount is not equal of the amount of Tg in the sample, **because thyroglobulin cannot be measured specifically by this measuring method. Therefore, the obtained result does not reflect the behavior of thyroglobulin, exactly**. Additionally, no disclosure concerning using thyroglobulin-specific antibody for the measurement is found.

Therefore, although Tarutani shows the ratio of [Con A-gel unbound Tg or Con A-gel bound Tg]/[the total Tg] from malignant thyroid tissue with that from a normal thyroid tissue and that from a benign thyroid tissue (Tarutani, page 855, Table II), the amounts used for calculating the ratio as thyroglobulin are derived from water soluble protein but not thyroglobulin itself. That is, **Tarutani does not disclose the measurement of thyroglobulin** using anti-thyroglobulin antibody and **the**

**true ratio of [Con A-gel unbound Tg or Con a-gel bound Tg]/[the total Tg].**

Applicant notes that, on page 854 of Tarutani, an anti-human Tg rabbit serum is used only for testing cross-reaction by examining the precipitin line with an anti-human Tg rabbit serum (page 854, column 1, lines 26-31). The procedure is not related to the measurement of Tg.

Tarutani suggests that thyroid tumors have an unusual ratio of Tg types. However, Tarutani does not show whether the Tg ratio is specific to thyroid tumor or not. Tarutani also does not indicate nor suggest that the relationship between the Tg ratio and malignancy (benign or malignant). There is found no disclosure in Tarutani that the measurement of Tg amount is useful for determining thyroid disease.

In Table II of Tarutani, Ratio of Tg(%) (Unbound) in Normal thyroid tissue of Group III is 0 (Unbound). The ratio in Papillary carcinoma (primary) of Group III is 0 (Unbound). From this result of Tarutani, one of ordinary skill in the art would not be able to predict that the ratio of [an amount of first type or second type of thyroglobulin]/[total amount of thyroglobulin] is useful for determining the malignancy of thyroid disease (benign or malignant).

**Applicant therefore submits that Tarutani has neither disclosure nor suggestion concerning determination of malignancy or thyroid tumor.**

Survilo

Survilo teaches that thyroglobulin samples from cancerous thyroids did not bind as strongly to Con A-Sepharose as did those from normal or goiterous thyroids.

However, Survilo **does not disclose nor suggest the measurement of thyroglobulin.** Determination of malignancy of thyroid tumor is not disclosed. Survilo **does not teach nor suggest comparison to benign thyroid adenoma.**

The cited references fail to disclose the measurement of thyroglobulin specifically by using either the anti-thyroglobulin antibody, or to disclose any method for determining malignancy of thyroid tumor by using the calculated ratio recited in the present claims. Moreover, the cited references do not disclose or suggest the relationship between the calculated ratio for normal, benign and malignant samples.

Applicant therefore submits that the present invention is novel and not obvious over Nakamura (U.S. Patent 5,571,729), Satomura (U.S. Patent 5,780,247), Yamamoto, Tarutani or Survilo, taken separately or in combination.

**Claims 70 and 71 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Katoh (U.S. Patent 5,591,589) in view of either Yamamoto (of record), Tarutani (of record) or Survilo for reasons of record.** (Office action paragraph no. 9)

The rejection of claims 70 and 71 is respectfully traversed, and reconsideration of the rejection is requested. Applicant has discussed the relevant teachings of Yamamoto, Tarutani and Survilo above, in response to the rejection of paragraph no. 8 of the Office action. Applicant here

additionally comments on Katoh.

Katoh

Katoh teaches methods for measuring the amounts of different types of glycoproteins that are different with respect to their pectin reactivity, and also the total amounts of the glycoprotein of interest. Katoh teaches the measurement of thyroglobulin by using a first antibody that has a property of bind to all the glycoproteins but does not bind to glycoproteins having a pectin attached thereto, and a second antibody that binds to all of the glycoproteins regardless of whether the pectin is also bound (claims 1 and 3). However, Katoh **does not disclose or suggest the measurement of thyroglobulin**. Katoh do not teach a relationship between differential thyroglobulin pectin-reactivity with malignancy of a thyroid tumor, at all. Determination of malignancy of thyroid tumor is not disclosed. Further, Katoh **does not teach nor suggest a comparison to benign thyroid adenoma**.

Applicant again argues that the cited references fail to disclose the measurement of thyroglobulin specifically by using either the anti-thyroglobulin antibody, or to disclose any method for determining malignancy of thyroid tumor by using the calculated ratio recited in the present claims. Moreover, the cited references do not disclose or suggest the relationship between the calculated ratio for normal, benign and malignant samples. Claims 70 and 71 are therefore novel and not obvious over Katoh, Yamamoto, Tarutani or Survilo, taken separately or in combination.

**Claim 73 is rejected under 35 U.S.C. §103(a) as being unpatentable over Canfield (WO 87/00289) in view of Yamamoto (of record).** (Office action paragraph no. 10)

The rejection of claim 3 is respectfully traversed, and reconsideration of the rejection is requested.

Applicant has discussed the teachings of Yamamoto above, in response to the rejection of paragraph no. 8 of the Office action. Applicant here comments on the teachings of Canfield.

Canfield

Canfield lists Tg as a compound that can be measured by the method shown in Canfield.

Actually, however, Canfield discloses a method for determining the presence of a soluble desialylated glycoprotein using a pectin and an antibody (Claim 1 etc.), and a method of diagnosing a disease such as **choriocarcinoma or hydatidiform mole using the presence of elevated levels of desialylated hCG (claim 16)**. In the specification, only the method for determining hCG is disclosed.

That is, Canfield does not teach nor suggest the **determination of malignancy of thyroid tumor by using the amount of Tg having a specific structure of a sugar chain**.

In the contrast, the characteristic of the present invention is "measuring Tg based on the difference of sugar chain structure", and then "determining the malignancy of the thyroid tumor using the result of the measurement." Such a concept cannot be suggested from Canfield, although Canfield lists Tg. That is, "the diagnosing method of choriocarcinoma or hydatidiform mole" of Canfield cannot apply easily to "the determination of malignancy of thyroid tumor" (the present

invention).

Determination of malignancy of thyroid tumor is not disclosed in Canfield. Further, Canfield does not teach nor suggest a comparison to benign thyroid adenoma.

Applicant again argues that the cited references fail to disclose the measurement of thyroglobulin specifically by using either the anti-thyroglobulin antibody, or to disclose any method for determining malignancy of thyroid tumor by using the calculated ratio recited in the present claims, and that the cited references do not disclose or suggest the relationship between the calculated ratio for normal, benign and malignant samples. Reconsideration of the rejection is respectfully requested.

**Claim 75 remains rejected under 35 U.S.C. §103(a) as being unpatentable over Katoh (supra) in view of Canfield (WO 87/00289) and further in view of Yamamoto (supra) for the reasons of record.**(Office action paragraph no. 11)

The rejection of claim 75 is respectfully traversed. Applicant's comments regarding the combination of Canfield and Yamamoto in response to the rejection stated in Office action paragraph no. 10 are applicable here, as well as Applicant's comments on Katoh in response to the rejection in Office action paragraph no. 9. Applicant submits that the combination of references does not provide the measurement of thyroglobulin specifically by using either the anti-thyroglobulin antibody, or to disclose any method for determining malignancy of thyroid tumor by using the calculated ratio recited in the present claims. Moreover, the cited references do not disclose or

suggest the relationship between the calculated ratio for normal, benign and malignant samples.

Reconsideration of the rejection is respectfully requested.

**Claims 51, 53, 54, 56, 58, 59, 68, 69 and 74 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 5-9 of U.S. Patent 5,780,247 in view of either Yamamoto (of record), Tarutani (of record) or Survilo.** (Office action paragraph no. 13)

The rejection of claims 51, 53, 54, 56 and 58 is moot in view of the cancellation of these claims without prejudice or disclaimer. The rejection of claims 59, 68, 69 and 74 is respectfully traversed.

In the rejection, the Examiner states that "the claimed inventions are an obvious species of method within the scope of claims 1 and 5-9 of U.S. Patent No. 5,780,247)." In response, Applicant refers to the above discussion of the teachings of Yamamoto, Tarutani, and Survilo, arguing that these references, even taken with the claims of U.S. Patent No. 5,780,247, do not disclose or suggest the specific limitations of the present claims.

**Claims 70 and 71 remain rejected under the judicially created doctrine of obviousness-type double patenting over claims 1 and 3 of U.S. Patent 5,591,589 in view of either Yamamoto (of record), Tarutani (of record) or Survilo.** (Office action paragraph no. 14)

The rejection of claims 70 and 71 is respectfully traversed. Applicant again refers to the above discussion of the teachings of Yamamoto, Tarutani and Survilo, arguing that these references, even taken with the claims of U.S. Patent No. 5,780,247, do not disclose or suggest the specific limitations of the present claims.

In view of the aforementioned amendments and accompanying remarks, the claims, as amended, are in condition for allowance, which action, at an early date, is requested.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicant's undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, Applicant respectfully petitions for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

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